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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,438	06/25/2007	Raymond Nadeson	210174.401USPC	9722

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EXAMINER	
JAGOE, DONNA A	

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1619	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,438	NADESON ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 43-50 are pending in this application.

Applicants' arguments filed May 21, 2010 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 43-45, 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al. (U) Regional Anesthesia and Pain Medicine: July/August, 1993, Vol. 18 No. 4 Page 4) and Grond et al. (V) (Pain, 79 1999 15-20)

Nickel et al. teach that flupirtine is a centrally acting analgesic (see introduction) and teach administration of flupirtine in combination with morphine for treatment of pain wherein it was demonstrated that the combination provided an increase in analgesic activity and furthermore flupirtine weakens morphine induced tolerance, physical dependence and behavior changes (see methods/results). It further states that flupirtine enhances the analgesic effects of opioids and this is confirmed in studies on cancer patients (see discussion).

Nickel et al. does not teach specifically treatment of neuropathic pain.

Grond et al. teach that neuropathic pain syndromes are one of the major problems of cancer pain treatment. Grond et al. teach employing an opioid analgesic (such as morphine) and non-opioid analgesics for the treatment of neuropathic pain stemming from cancer (see abstract and see table 1).

Grond et al. does not teach administration of flupirtine.

It would have been obvious to employ the combination of flupirtine and an opioid analgesic, such as morphine for the treatment of neuropathic pain, especially from cancer pain, motivated by the teaching of Nickel et al. who teach that flupirtine is a centrally acting analgesic (see introduction) that enhances the analgesic effects of opioids, such as morphine for treatment of cancer pain, and the teaching of Grond et al. who teach that neuropathic pain syndromes are one of the major problems of cancer pain treatment and teach that opioids are often combined with non-opioid agents in the treatment of cancer pain.

Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al. (U) Regional Anesthesia and Pain Medicine: July/August, 1993, Vol. 18 No. 4 Page 4) and Grond et al. (V) (Pain, 79 1999) as applied to claims 43-45, 48 and 49 above, and further in view of Perovic et al (Neurodegeneration, Vol. 4 pages 369-374 (1995)).

Perovic et al. teach that flupirtine is a clinically safe compound with drowsiness reported in only 10% of cases (page 373, column 2). Since the dosage of the opioid is not disclosed, then the claim encompasses an almost negligible amount of opioid and as such overt sedation would not occur since it is dose related.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ a non sedating combination of flupirtine and an opioid motivated by the teaching of Perovic et al. that flupirtine caused drowsiness in only 10 % of cases combined with the well known fact that sedation of opioid analgesics is dose related and since the claims do not disclose the dosage, they encompass a negligible amount of

opioid. Further, Nickel et al. teach that flupirtine weakens morphine induced behavior changes (see methods/results). One having ordinary skill in the art at the time the invention was made would reasonably deduce that sedation is one of the primary behavior changes that morphine induces.

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al. (U) Regional Anesthesia and Pain Medicine: July/August, 1993, Vol. 18 No. 4 Page 4) and Grond et al. (V) (Pain, 79 1999) as applied to claims 43-45, 48 and 49 above, and further in view of Devulder at al. (U).

Devulder et al. teach the dose of flupirtine for treatment of neuropathic (central) pain is 300-600 mg/day. The instant claim is drawn to 0.5mg/kg to about 20 mg/kg of body weight. Translating the dose of Devulder et al. to mg/kg based on an average 80 kg human the dosage would be 3.75 mg/kg[1] to 7.5 mg/kg[2]. This dosage amount is encompassed by the claimed amount of 0.5 mg/kg to about 20 mg/kg. A prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005).

It would have been made obvious to one of ordinary skill in art at the time it was made to employ 0.5 mg/kg to about 20 mg/kg of flupirtine in the composition combined

[1] 300 mg / 80 kg = 3.75 mg/kg
[2] 600 mg / 80 kg = 7.5 mg/kg

with another opioid agent, such as morphine to treat neuropathic pain motivated by the teaching of Nickel et al. and Grond et al (supra) and the teaching of Devulder et al. who teaches that the dosage of flupirtine for central (neuropathic) pain is 300 to 600 mg/day (approximately 3.75 mg/kg to about 7.5 mg/kg).

Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nickel et al. (U) Regional Anesthesia and Pain Medicine: July/August, 1993, Vol. 18 No. 4 Page 4) and Grond et al. (V) (Pain, 79 1999) as applied to claims 43-45, 48 and 49 above, and further in view of Cleary (Cancer Control, 2000).

Cleary teaches that cancer pain can have a neuropathic component (page 122, column 2 "character"). It further identifies specific cancers for which such neuropathies occur, such as colon cancer, non-small cell lung cancer and multi-organ system failure associated with cancer (page 121, column 2 bridging to page 122). Cleary also discloses that although opioids are the mainstay of cancer pain management, adjunct therapy is recommended. Adjuvant medications may result in a decrease in opioid dose with an associated decrease in side effects and adjuvant therapy is often useful with opioids in the treatment of neuropathic pain. (page 127, column 2).

Response to Declaration

The Declaration under 37 CFR 1.132 filed May 21, 2010 is insufficient to overcome the rejection of claims 43-45, 48 and 49 based upon Nickel et al and Grond et al.; claim 46 based upon Nickel et al. and Grond et al in view of Perovic et al; claim 47

based upon Nickel et al. and Grond et al. in view of Devulder et al.; and claim 50 based upon Nickel et al. and Grond et al. in view of Cleary, as set forth in the last Office action because: It refer(s) only to the system described in the above referenced application and not to the individual claims of the application. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716. Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967) (resultant decrease of dental enamel solubility accomplished by adding an acidic buffering agent to a fluoride containing dentifrice was expected based on the teaching of the prior art); *Ex parte Blanc*, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989) (Claims at issue were directed to a process of sterilizing a polyolefinic composition which contains an antioxidant with high-energy radiation. Although evidence was presented in appellant's specification showing that particular antioxidants are effective, the Board concluded that these beneficial results would have been expected because one of the references taught a claimed antioxidant is very efficient and provides better results compared with other prior art antioxidants.). In this case, Nickel et al teach treatment of cancer pain comprising the combination of flupirtine and morphine and also teach that the combination enhances the analgesic effects of opioids and furthermore flupirtine weakens morphine induced tolerance, physical dependence and behavior changes (see methods/results). Additionally, Grond et al teach that cancer pain is most frequently

neuropathic and further teach the combination of opioids with nonopioids for neuropathic pain.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Response to Arguments

Applicant traverses the rejections and states that the examiner has not satisfied the requirements of non-obviousness over the cited references. Applicant further states that Nickel et al. provides no expectation that the combination of flupirtine and an opioid would have been effective at treating neuropathic pain, specifically because it is well established that agents which target one type of pain do not necessarily work in other forms of pain. In response, Applicants' exemplify cancer pain as the model for neuropathic pain. Nickel et al. teach that **flupirtine enhances the analgesic effects of opioids** and this is confirmed in studies on **cancer patients** (see discussion). The secondary reference, Grond et al., teach that neuropathic pain syndromes are one of the major problems of cancer pain treatment. Applicant states that Nickel et al. merely hypothesize that flupirtine would be effective to enhance the analgesic effects of opioids. In response, Nickel et al. state that "Initial studies in cancer patients confirm these expectations". This means that the combination of flupirtine and morphine was administered to cancer patients and the hypothesis is confirmed. Applicant states that the Grond reference teaches thousands of non-opioids. In response, Nickel et al. teach specifically the combination of flupirtine and morphine for

cancer pain which is most often neuropathic pain as confirmed by Grond et al. Applicant states that synergism is evidence of non-obviousness, however, Nickel et al teach the same synergism with the same combination of morphine and flupirtine. Applicants' reliance on Shimoyama et al to allegedly provide evidence of surprising results is not persuasive. In reference to arguments drawn to the Declaration of Dr. Goodband, it has been considered supra. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., flupirtine in combination with an opioid allows a 90% reduction in the amount of either drug in order to obtain an analgesic effect for neuropathic pain) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YVONNE L. EYLER/ Donna Jagoe /D. J./

Supervisory Patent Examiner, Art Unit 1619

Examiner
Art Unit 1619

May 28, 2010